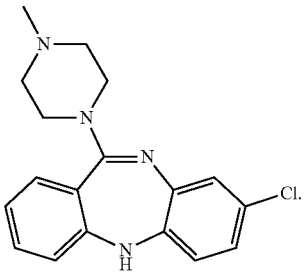
CLOZAPINE FOR THE TREATMENT OF A IMMUNOGLOBULIN DRIVEN B CELL DISEASE

TECHNICAL FIELD

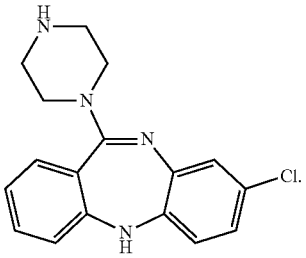
[0001] This invention relates to a compound and pharmaceutical compositions containing such compound for use in the treatment or prevention of a pathogenic immunoglobulin driven B cell disease with a T cell component.

BACKGROUND TO THE INVENTION

[0002] The compound associated with this invention is known as clozapine i.e. the compound of the following structure:



[0003] Clozapine has a major active metabolite known as norclozapine (Guitton et al., 1999) which has the following structure:



[0004] Clozapine is known as a treatment for resistant schizophrenia. Schizophrenia is an enduring major psychiatric disorder affecting around 1% of the population. Apart from the debilitating psychiatric symptoms it has serious psychosocial consequences with an unemployment rate of 80-90% and a life expectancy reduced by 10-20 years. The rate of suicide among people with schizophrenia is much higher than in the general population and approximately 5% of those diagnosed with schizophrenia commit suicide.

[0005] Clozapine is an important therapeutic agent and is included on the WHO list of essential medicines. It is a dibenzo-diazepine atypical antipsychotic, and since 1990 the only licensed therapy in the UK for the 30% of patients with treatment-resistant schizophrenia (TRS). It shows superior efficacy in reducing both positive and negative symptoms in schizophrenic patients and is effective in approximately 60% of previously treatment refractive patients with a significant reduction in suicide risk. The National Institute for Health and Clinical Excellence (NICE) guideline recommends adults with schizophrenia which has not responded adequately to treatment with at least 2 antipsychotic drugs (at least one of which should be a non-clozapine second generation antipsychotic) should be offered clozapine.

[0006] Clozapine is associated with serious adverse effects including seizures, intestinal obstruction, diabetes, thromboembolism, cardiomyopathy and sudden cardiac death. It can also cause agranulocytosis (cumulative incidence 0.8%); necessitating intensive centralised registry based monitoring systems to support its safe use. In the UK there are three electronic registries (www.clozaril.co.uk, www.denzapine.co.uk and www.ztas.co.uk) one for each of the clozapine suppliers. Mandatory blood testing is required weekly for the first 18 weeks, then every two weeks from weeks 19-52 and thereafter monthly with a 'red flag' cut-off value for absolute neutrophil count (ANC) of less than 1500/4 for treatment interruption.

[0007] In 2015, the Federal Drug Administration (FDA) merged and replaced the six existing clozapine registries in the United States combining data from over 50,000 prescribers, 28,000 pharmacies and 90,000 patients records into a single shared registry for all clozapine products, the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (www.clozapinerems.com). Changes were introduced lowering the absolute neutrophil count (ANC) threshold to interrupt clozapine treatment at less than 1000/4 in general, and at less than 500/4 in benign ethnic neutropenia (BEN). Prescribers have greater flexibility to make patient-specific decisions about continuing or resuming treatment in patients who develop moderate to severe neutropenia, and so maximize patient benefit from access to clozapine.

[0008] Schizophrenia is associated with a 3.5 fold increased chance of early death compared to the general population. This is often due to physical illness, in particular chronic obstructive pulmonary disease (COPD) (Standardised Mortality Ratio (SMR) 9.9), influenza and pneumonia (SMR 7.0). Although clozapine reduces overall mortality in severe schizophrenia, there is a growing body of evidence linking clozapine with elevated rates of pneumonia-related admission and mortality. In an analysis of 33,024 patients with schizophrenia, the association between second generation antipsychotic medications and risk of pneumonia requiring hospitalization was highest for clozapine with an adjusted risk ratio of 3.18 with a further significant increase in risk associated with dual antipsychotic use (Kuo et al., 2013). Although quetiapine, olanzapine, zotepine, and risperidone were associated with a modestly increased risk, there was no clear dose-dependent relationship and the risk was not significant at time points beyond 30 days (Leung et al., 2017; Stoecker et al., 2017).

[0009] In a 12 year study of patients taking clozapine, 104 patients had 248 hospital admissions during the study period. The predominant admission types were for treatment of either pulmonary (32.2%) or gastrointestinal (19.8%) illnesses. The commonest pulmonary diagnosis was pneumonia, (58% of pulmonary admissions) and these admissions were unrelated to boxed warnings (Leung et al., 2017).

[0010] In a further nested case control study clozapine was found to be the only antipsychotic with a clear dose-dependent risk for recurrent pneumonia, this risk increased on re-exposure to clozapine (Hung et al., 2016).

[0011] While these studies underscore the increased admissions or deaths from pneumonia and sepsis in patients taking clozapine over other antipsychotics, the focus on extreme outcomes (death and pneumonia) may underesti-